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Cleveland Clinic Quarterly

Volume 26 JANUARY 1959 No. 1

EPISODIC HEPATIC ENCEPHALOPATHY: A PROBLEM OF ALL SPECIALTIES

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COMA is a well-recognized and much-feared complication of hepatic disease, especially of cirrhosis. In recent years the spectrum of neuropsychiatric symptoms due to hepatic disease, varying from subtle personality change, episodic stupor, and transient coma, to chronic dementia, has been more fully appreciated.[1] We are reporting four cases of hepatic encephalopathy which were not suspected either by the referring physicians or by the clinicians here who first examined the patients. The first patient was admitted to the vascular service for study of edema of the lower half of the body and suspected "thromboembolic strokes." The second patient was admitted to the proctologic service because of severe rectal hemorrhage associated with possible small strokes. The third patient was admitted to the gastrointestinal service because of jaundice, splenomegaly, and recurrent anemia after several gastrointestinal hemorrhages. The fourth patient was admitted to the neurosurgical service because of stupor thought to be the result of a cerebral injury incurred in an automobile accident. In each of these patients the elevation of the blood ammonium nitrogen (hereinafter designated as B.A.N.) was of decisive importance in the diagnosis. The normal range was from 36 μg. to 75μg. per 100 ml. The blood was drawn into syringes containing heparin, and the determinations

were performed within 20 minutes. The method was a modification (by W. R. F.) of the Conway Method.

Subtle personality change may escape notice for long periods, and its relationship to known hepatic disease may not be recognized or the mental disorder may progress to a dementia and the established hepatic disorder may be forgotten. Instances of chronic dementia have been described in which hepatic disease was present, and the relatively simple treatment of reducing or temporarily withdrawing dietary protein has effected a return to a normal mental state.[2] Since increased protein intake is necessary to combat the underlying hepatic disorder, other therapeutic measures to permit this are necessary; these will be described.

The current concept of the mechanism of episodic stupor is that in hepatic disease the products of accelerated bacterial action on ingested proteins in the digestive tract not only are poorly detoxified by the abnormal liver, but also bypass the liver, by the collateral circulation, to exert a harmful effect on the central nervous system. Although other toxic substances may be involved, ammonia is the only toxic product demonstrable in most patients, and measurable with reasonable accuracy by standard methods.

After portacaval anastomosis the blood, and consequently ammonia, can bypass the liver more readily. Thus, episodes of stupor may occur more readily with an overload of dietary protein with only minor impairment of hepatic function; however, patients can adjust to a higher systemic concentration of ammonia so that such episodes may not recur frequently. Gastrointestinal hemorrhage in, and the administration of ammonium compounds to, patients with hepatic disease may impose an excessive load of ammonia on the liver, and result in coma. Some diuretic agents such as chlorothiazide* and acetazolamide† may also precipitate hepatic coma.

There are two possible mechanisms by which excessive ammonia and other possible toxic agents can reach the general circulation from the intestine. These are through a severely diseased liver as in severe hepatitis, and through various collateral vessels that bypass the hepatic parenchyma as in cirrhosis. The path through collateral vessels is the mechanism involved in most clinical instances of hepatic encephalopathy; thus Sherlock, Summerskill, White, and Phear[2] have termed this "portal-systemic encephalopathy."

Our four cases illustrate some of the variations of the syndrome of hepatic encephalopathy. Three patients had demonstrable collateral circulation and may therefore be considered to have had portal-systemic encephalopathy. In one patient collateral circulation was not demonstrated although it may have been present.

Case Reports

Case 1. A 46-year-old white man was admitted to the Cleveland Clinic Hospital, on

**Diuril (chlorothiazide), Merck Sharp & Dohme.*
†Diamox (acetazolamide), Lederle Laboratories.

December 17, 1957, to the peripheral vascular disease service with a history of recurrent swelling of the legs, a transient cerebrovascular disorder, thrombophlebitis, and of having had ligations of the saphenous and of the femoral vein. Twenty-six months previously (October, 1955) he had swelling of one leg and the scrotum, and was hospitalized for one month for thrombophlebitis, and for hepatic and renal diseases. Alcoholic beverages, used to "excess" up to that time, had been discontinued because of a hepatic disorder. Sixteen months later, ten months before examination here, swelling of the legs and of the scrotum recurred, but responded to mercurial diuretics. Three months later an episode of stupor, slurred speech, and incoordination was diagnosed as cerebral thrombosis without residual neurologic deficit. The next month another episode was more intensively investigated with pneumoencephalography; the diagnosis was the same. In the next month, superficial thrombophlebitis was treated by ligations of the bilateral saphenous and right femoral veins because of the above-described episodes of slurred speech and incoordination which were considered "small strokes from emboli." For the next five months the patient continued to have swelling of the legs and of the scrotum, and to receive mercurial diuretics. There was only slight response to treatment, and the patient was unable to return to work.

At physical examination here he weighed 232 pounds, and his blood pressure was 140/86 mm. of Hg. The patient was alert and cooperative. There were no spider nevi or icterus. The heart and lungs were normal. The abdominal wall was edematous and the abdominal organs were not palpable. There was severe edema of the penis, the scrotum, and the legs. After the loss of edema fluid following intensive treatment, examination disclosed a descent of the liver one fingerbreadth below the right costal margin, and of the spleen four fingerbreadths below the left costal margin. There were no signs of neurologic disorder.

Roentgen findings of the skull and chest were normal. An esophogram showed no evidence of varices. An electrocardiogram showed no abnormality.

According to initial laboratory studies: the hemoglobin was 10 gm. per 100 ml., with 4,000 leukocytes and a normal differential count. Urinalysis showed a trace of albumin and many erythrocytes. The culture of the urine showed no organisms. Fasting blood sugar was 83 mg., blood urea 33 mg., plasma creatinine 0.5 mg., serum cholesterol 174 mg., serum albumin 1 gm., serum globulin 4.5 gm. per 100 ml.; serum bilirubin, direct was 0.3 mg., and indirect was 1.5 mg. per 100 ml. Bromsulphalein retention was 9 per cent in 45 minutes. The serologic test for syphilis was negative. Thymol turbidity was 10 units. The prothrombin time was 18 seconds (68 per cent of normal). The cephalin-cholesterol flocculation test was 4 plus in 24 hours. The zinc sulfate turbidity test was 21 units.

Progress laboratory findings showed a striking increase in Bromsulphalein retention after the first month, but no other notable change. The cephalin-cholesterol flocculation test continued to be 4 plus and remained so three months after the patient was discharged. Serum proteins were temporarily increased by parenteral injections of albumin, subsequently declined, and later increased slightly. The number of blood platelets was decreased, the count being from 30,000 to 90,000 per cubic millimeter, which was ascribed to probable hypersplenism.

On the third day in the hospital a venogram showed evidence of a normal inferior vena cava.

The patient was treated with mercurial diuretics and in one week lost 22 pounds in weight; he became confused and stuporous. A gross tremor was noted and also fetor hepaticus. He was given a low-protein (from 20 to 30 gm.), low-sodium (0.5 gm.), high-carbohydrate diet; orally neomycin sulfate tablets* (500 mg.), four times daily; sodium glutamate (25 gm. in 500 ml. of 10 per cent dextrose solution) and arginine hydrochloride (25 gm. in 500 ml. of 10 per cent dextrose solution) intravenously daily. He gradually improved. Arginine glutamate† (25 gm. in 500 ml. of 10 per cent dextrose) was sometimes substituted for sodium glutamate and arginine hydrochloride. Administration of mercurial diuretics was continued. He was also given albumin (25 gm.) daily intravenously for several days and two units of whole blood. After two weeks he was mentally clear and his weight had decreased 25 pounds more (a total loss of 47 pounds of edema fluid). During a period of 10 days the protein intake was again gradually increased to 110 gm. daily and neomycin was omitted. The patient again lapsed into a semicomatose condition; a program similar to that described above was reinstated.

These episodes were characterized by mental confusion, incoordination, tremor of the body, flapping tremor of the hand, presence of Babinski's sign (variably right or left foot), hyperactive deep-tendon reflexes, and bilateral sustained clonus of the ankles. A significant feature of these episodes was the transient nature of the neurologic manifestations. Although neurologic examination showed definite abnormality at the time of each episode of stupor, a few days after each episode findings were equivocal or normal. The electroencephalograms likewise showed a striking change *(Fig. 1)*.

The patient again recovered. He was discharged and was directed to follow a 120-gm. protein diet with neomycin (0.5 gm.) four times daily. He returned in four days, stuporous and tremulous; laboratory findings were similar to those described above; the B.A.N. was 264 μg. per 100 ml.

A low-protein (30-gm.) diet, neomycin orally (1 gm.) every three hours, and arginine hydrochloride intravenously were given. Later, 25,000 units of bacitracin was administered orally every six hours. The patient made rapid symptomatic progress and became normally alert. The B.A.N. decreased to 183 μg. per 100 ml., and the patient was discharged on the fifth day, with the advice to follow an 80-gm. protein diet, neomycin (0.5 gm.) four times daily, and bacitracin (25,000 units) orally four times daily.

In the out-patient department he made satisfactory progress. The B.A.N. concentration remained abnormally high in the first month, but the electroencephalogram was normal. Later the concentration of B.A.N. declined, although it remained elevated. Lymphedema of the legs and thighs, which persisted in spite of diuresis and loss in weight, was successfully controlled by pneumatic massage and full-length elastic stockings. After one month the patient returned to work for the first time in almost two years. In two months the patient started full-time work, and although requiring regular treatment, including a neomycin sulfate tablet (0.5 gm.) four times daily, a tablet of neomycin (25 gm.) and bacitracin (2,500 units) ‡ four times daily, he is much improved, and has continued so to the last follow-up examination in October, 1958. The B.A.N.

**Mycifradin (neomycin) sulfate tablets, The Upjohn Company.*

†Modumate (arginine glutamate) was provided through the courtesy of Abbott Laboratories.

‡Neobacin (neomycin 25 mg., and bacitracin 2,500 units) tablets were supplied through the courtesy of Reed & Carnrick.

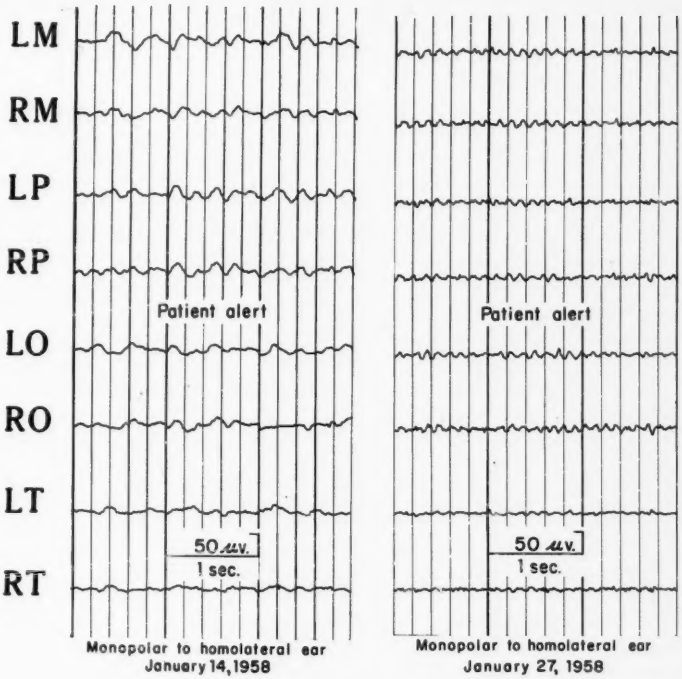

Fig. 1. Case 1. Electroencephalograms before and after treatment for episodic stupor.

has remained at about 140 μg. per 100 ml. despite clinical improvement.

Comment. This case emphasizes the importance of recognizing the syndrome of episodic stupor. The description of the previous episodes, which were considered recurrent cerebral thromboses without residual effects, was identical with that of the episodes of portal-systemic stupor that we observed. The two recurrences of these episodes after the institution of a high-protein diet suggest the probability that previously the patient had an intermittent type of high-protein intake with episodes of stupor following periods of increased intake, with these in turn being relieved by the decreased protein intake attendant upon such stupor. The striking change in the electroencephalogram after treatment is noteworthy. The triphasic waves that have been considered most typical of hyperammoniemia[3, 4] are not present, but the diffuse, abnormal changes are definite, and the complete disappearance after treatment is dramatic.

The chronic renal disorder present in this patient had no apparent relationship to the episodic stupor. There were no significant variations in renal function, electrolyte imbalance, azotemia, or other evidence of renal failure.

Case 2. A 53-year-old white woman was transferred on December 26, 1957, to the

proctologic service of the Cleveland Clinic Hospital from another hospital where she had been for one month because of weakness, loss of weight, recurrent rectal bleeding, and a brief episode of hepatic coma that was said to have responded to cortisone treatment. Two years previously a large liver was noted.

On admission to the Cleveland Clinic Hospital, the patient had a temperature of 99° F., a pulse of 80, and a blood pressure of 120/70 mm. of Hg. Mild icterus was present, but no spider nevi were seen. The liver was nodular and descended 10 cm. below the right costal margin, and the spleen descended 6 cm. below the left costal margin. Neither edema nor ascites was present.

Laboratory findings included: bromsulfalein retention 15 per cent in 45 minutes; cephalin-cholesterol flocculation 4 plus; thymol turbidity 14 units; bilirubin, direct, 0.3 mg., indirect, 0.8 mg.; serum albumin 2.4 gm., and serum globulin 4.6 gm. per 100 ml. Prothrombin time was 68 per cent of normal (18 seconds; normal, 14 seconds); bleeding time 1½ minutes; coagulation time 16 minutes. After a barium meal, roentgenograms of the esophagus and stomach showed no evidence of varices, barium enema showed only diverticula. Esophagoscopy revealed no varices. Proctoscopy showed greatly dilated mucosal veins well above the rectal ampulla. Histologic study of specimens of a needle biopsy of the liver showed severe hepatic cirrhosis with features of both the postnecrotic and nutritional types.

The patient was discharged and was advised to follow a program of treatment for hepatic cirrhosis. She was readmitted two months later; she had gained 14 pounds in weight and had slight edema of the ankles. Additional history from relatives disclosed that two years previously she had undergone certain changes, among which slow, deliberate speech, slow motions and actions, and prolonged reading time were noted. Six months before admission the patient had deep stupor after rectal bleeding, had fallen and fractured some ribs, but had no recollection of doing so. At re-examination the B.A.N. was 210 μg. per 100 ml.; serum albumin had increased to 3.2 gm., and serum globulin was about the same at 4.5 gm. per 100 ml.; bromsulfalein retention value also was higher, 29 per cent in 45 minutes. An electroencephalogram showed abnormal, diffuse changes with slow activity more pronounced on the left than on the right side.

The patient was started on a course of treatment that included neomycin (0.5 gm.) four times daily for three days, then neomycin (50 mg.) and bacitracin (5,000 units) four times daily in a special tablet. A high-protein diet and intravenous injections of albumin were also instituted. In four days the B.A.N. decreased to 104 μg. per 100 ml. and the patient became much more alert; the examinations and her progress under treatment indicated that prolonged hepatic encephalopathy had existed.

A portacaval shunt and a cholecystectomy were performed. The diagnosis of postnecrotic cirrhosis with portal hypertension was confirmed. At discharge the patient was advised to follow a high-protein diet and to take a small daily dose of neomycin. The neomycin was discontinued after one month, after which time the diet was not followed carefully. She made satisfactory progress for two months, and then was reported to have become gradually weaker and more lethargic. During this period of increasing weakness and lethargy she had eaten larger quantities of meat than usual.

She was readmitted to the hospital after three months. Memory deficit, psychic apraxia, presence of Verpus (snout) reflex and left Babinski's sign, and a grossly asym-

metric electroencephalogram all suggested to the neurologist the presence of a chronic cerebral disease. The patient was given neomycin (0.5 gm.) four times daily, and daily infusions of arginine hydrochloride (25 gm.). Within a few days she improved greatly, although dietary protein was not restricted. The B.A.N. varied from 142 μg. to 274 μg. per 100 ml. and gave no evidence of an over-all decrease.

Two months later the patient was asymptomatic, although the B.A.N. was 160 μg. per 100 ml.; four months later the B.A.N. was 110 μg. She was taking 120 gm. of protein daily, Neobacin tablets three times a day, and was alert and well.

Comment. This case demonstrates a chronic disorder of the personality with definite decrease in intellectual function and altered affect. A special aspect of the problem was the striking collateral circulation provided by the dilated sigmoidal veins. After a portacaval shunt, increasing stupor developed. The interesting point was that because she knew she was not doing well the patient herself increased the consumption of meat. The immediate response to treatment was especially noteworthy, although the neurologist considered the symptoms indistinguishable from chronic cerebral disease.

Case 3. A 35-year-old white man was admitted on October 14, 1957, to the Cleveland Clinic Hospital, to the gastroenterologic service, because of recurrent jaundice and anemia following recent hematemesis and melena. Four years previously, at another hospital, he had a cholecystoduodenostomy performed for obstruction of the common bile duct. At physical examination, splenomegaly, and jaundice without hepatomegaly were noteworthy. Studies of specimens of a needle biopsy of the liver showed the presence of moderate posthepatitic cirrhosis. Esophograms showed definite evidence of varices *(Fig. 2)*. While studies were in progress the patient had a recurrent severe upper

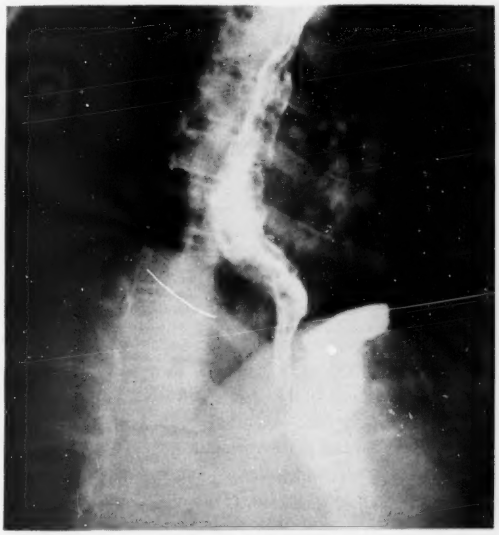

Fig. 2. Case 3. Esophogram showing evidence of extensive varices in a patient who had episodic stupor.

gastrointestinal hemorrhage that was controlled by balloon tamponade using a Sengstaken-Blakemore tube. With satisfactory hepatic function and repeated hemorrhages, surgical management of portal hypertension was elected. Splenoportography showed marked dilatation of the portal vein with extensive esophageal and gastric varices. An end-to-side portacaval shunt was constructed; immediately, portal pressure as well as the size of the varices decreased. The postoperative course was satisfactory, and 20 days after operation the patient was discharged with the advice to follow a program for treatment of cirrhosis, including a 120-gm. protein diet daily.

The patient returned about three months later, reporting a steady gain in weight and strength, but with an increasing inability to concentrate, and soreness and stiffness of the muscles in walking. His family physician had noted some loss of affect. Examination showed a masklike facies, rigidity of the head and arms while walking, and a generalized, fine, intermittent tremor. Administration of prochlorperazine* tablets, which had been given in a dosage of 5 mg. four times daily, was discontinued, but there was no change within 24 hours. At that time the arterial B.A.N. was 167 μg. Neomycin tablets were given in a dosage of 2 gm. four times daily, and in 24 hours the patient improved dramatically; he was alert, without tremor, and with less soreness of muscles. The B.A.N. decreased to 85 μg. during the one day. A few days later the patient was discharged with the advice to follow the same high-protein diet, but with 0.5 gm. of neomycin for a week, then two Neobacin tablets with meals and at bedtime. Thereafter he resumed full-time work without difficulty and in four months was able to discontinue the taking of antibiotics.

Comment. This case likewise demonstrates the gradual onset of a personality change after portacaval shunt, and then a striking response to therapy. The esophageal varices were well demonstrated in the roentgen study of the esophagus, indicating the extent of collateral circulation present before the portacaval shunt, when there was no evidence of hepatic encephalopathy.

Case 4. A 55-year-old white man was transferred on March 5, 1958, to the Cleveland Clinic Hospital for neurosurgical care because of stupor occurring the day after a splenectomy that was performed at another hospital for traumatic laceration of the spleen sustained in an automobile accident. There had been no initial period of unconsciousness. It was learned (sometime later) that the history included excessive use of alcoholic beverages, a tendency to fall asleep "too easily," and an episode of jaundice in childhood.

Although not alert at the time of admission here, the patient was able to cooperate for examination. The blood pressure was 120/80 mm. of Hg. A mild fetor, and a flapping tremor of the outstretched hands were present. The liver descended 6 cm. on inspiration. Laboratory findings included: B.A.N. 121 μg. per 100 ml.; bromsulfalein retention 12 per cent in 45 minutes; serum albumin 4.1 gm.; serum globulin 2.9 gm.; serum bilirubin, direct none, indirect 0.8 mg.; and blood urea 101 mg. per 100 ml. At lumbar puncture, normal cerebrospinal fluid was found and the dynamics were normal. An electroencephalogram showed abnormally slow waves without dominant rhythmi-

**Compazine (prochlorperazine), Smith, Kline & French.*

city, waves of varying frequency (from 4 to 6 per second), and rhythmicity on a varying base line.

The patient was given arginine hydrochloride (25 gm. in 500 ml. of 10 per cent dextrose in distilled water) intravenously every six hours for one day, and then once daily for five days. He became much clearer mentally after one day of treatment. The flapping tremor and the fetor disappeared.

The patient subsequently showed gradual decline in blood hemoglobin content, and the symptoms and signs of abdominal sepsis developed. At operation, multiple "stress" ulcers of the stomach and cecum were found along with a perforation of the cecum. A hemigastrectomy, closure of the perforation of the cecum, and a tube cecostomy were performed. Thereafter the patient's course was rather stormy, but he gradually improved. Eventually the degree of improvement permitted needle biopsy of the liver. The histopathologic diagnosis was slight fatty change and chronic inflammation in the portal areas. Two months later the patient had completely recovered and had resumed full activity.

Comment. This case demonstrates the effect of a combination of gastrointestinal bleeding, shock, and abdominal trauma on a mildly diseased liver. The ammonia formed in the intestinal tract was undoubtedly not metabolized by the liver because of its temporarily depressed function.

Although the patient was referred to the Cleveland Clinic originally because of the possibility of cerebral injury, none was found.

Uremia must be considered in the differential diagnosis of disease in this patient, since the blood urea was increased. The flapping tremor may occur in uremia, but hyperammoniemia does not. The response to arginine also favors the diagnosis of hyperammoniemic (hepatic) encephalopathy.

Diagnosis

The diagnosis of hepatic encephalopathy necessitates a greater awareness of its varied symptoms, and more understanding of the multiple neurologic and personality changes that can occur. The lack of recognition of this syndrome is dramatically illustrated by the experience of Sherlock and associates[2] who described several patients having "episodic stupor" who had been placed in mental institutions. As the patients became stuporous they stopped eating, thus decreasing the dietary protein intake. With a decrease in protein intake, the patients regained their mental faculties, only to lapse into stupor again as they again ate more protein; hence the term "episodic stupor."

This condition occurs after operations for portacaval shunt, and in patients with portal hypertension in whom venous shunts and collateral circulation have developed. The encephalopathy is episodic, frequently being precipitated by gastrointestinal hemorrhage, trauma, infection, or excess dietary protein intake.

Episodic hepatic encephalopathy, as well as many instances of acute hepatic coma such as those precipitated by massive gastrointestinal hemorrhages, differs clinically from hepatic coma that develops spontaneously in the late stages of chronic hepatic disease, as in Laennec's cirrhosis. The prognosis in episodic hepatic

encephalopathy is good, *provided the condition is recognized and treatment is instituted.* Repeated episodes can occur with the patient recovering and being left with no residual cerebral or neurologic damage. The prognosis of hepatic coma occurring in the late stages of chronic hepatic disease usually is poor and the episode is fatal. However, ammonia intoxication may be a factor and treatment should be attempted.[5]

Bizarre and shifting abnormal neurologic changes, personality disorders, loss of affect, loss of memory, and stupor in a patient with hepatic disease should suggest the diagnosis of episodic hepatic encephalopathy. These changes are almost pathognomonic in any patient with portal hypertension, or in a patient who has had a portacaval shunt. According to current concepts, the diagnosis is confirmed by the finding of an abnormally increased amount of B.A.N.. The concentration of B.A.N. usually approaches normal as the patient improves with treatment. Electroencephalographic changes also can be of diagnostic help.

Treatment

Until the cause of hepatic encephalopathy is more clearly understood, treatment will continue to be largely supportive and nonspecific. At present, in selected cases, some specific measures seem applicable. Details of treatment are presented fully in other reports[5, 6] and will be reviewed only briefly here.

Episodic stupor or suspected chronic "hepatic" dementia may be treated by temporary withdrawal of protein from the diet. Neomycin, 1 or 2 gm. every six hours, is given by mouth to suppress intestinal bacteria, thereby preventing enzymatic degradation of protein and the formation of ammonia. Vitamin supplements, particularly vitamins B, C, G, and K are administered. The patient is sustained with carbohydrate foods and, after improvement is noted, protein is added to the diet slowly in increasing amounts. Many patients will tolerate a high-protein diet as long as neomycin is continued. Later, moderate protein intake may be tolerated without neomycin. Prevention of recurrence of episodic stupor involves adjustment of the protein in the diet to the tolerance of the patient, along with the general measures for the chronic hepatic disease present. Neomycin may be necessary indefinitely to permit satisfactory protein intake.

In deepening or severe stupor, or in those cases in which a flapping tremor of the hands with the arms outstretched heralds the onset of coma, arginine or glutamic acid should be administered intravenously, arginine hydrochloride (25 gm.), arginine glutamate or sodium glutamate (23 gm. in 500 ml. of 10 per cent dextrose in water) may be given as often as every six hours. Arginine and glutamic acid combine with ammonia and facilitate its excretion. Acidosis from the arginine hydrochloride, or edema from the sodium glutamate may limit such therapy. Thus, arginine glutamate, may prove to be preferable.

Hepatic coma as a complication of bleeding esophageal varices demands comprehensive treatment.[6] The blood must be quickly removed from the gastroin-

testinal tract. Since the Sengstaken-Blakemore tube usually will be inserted for esophageal tamponade in such cases, aspiration of blood pooled in the stomach, and administration of medications, are readily accomplished. Castor oil or magnesium sulfate should be given through the tube and, later, administration of neomycin should be started. The colon should be emptied by means of cleansing enemas. Other aspects of treatment include supportive measures, surgical treatment, and the therapy of hepatic disease per se.[5, 7]

Summary

Encephalopathy due to hepatic disease may be manifested by episodic stupor or chronic change in the personality as well as by coma. Since these various manifestations of encephalopathy may appear as complications of other diseases, especially of acute, severe disorders, all physicians ought to be aware of their significance. Episodic stupor, unlike many instances of terminal hepatic coma, may be reversible. Specific measures to diminish formation of ammonia in the intestinal tract and to lower excessive amounts in the blood are utilized along with general measures for hepatic disease.

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CHLORPROPAMIDE,* A NEW DRUG FOR DIABETES MELLITUS: CLINICAL STUDIES

A Preliminary Report

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SINCE 1942, when sulfonylurea derivatives were found to have hypoglycemic action, a large number of related compounds have been developed and are being used in diabetic patients. The most recent of these is chlorpropamide.*[1-7]

The basic molecular structure of chlorpropamide is similar to that of other sulfonylureas, but the addition of a chlorine atom has made the action of the drug more prolonged. In man, the plasma concentration of chlorpropamide has decreased by one half in approximately 36 hours,[8, 9] whereas that of tolbutamide has decreased by one half in four hours.[10] As a result, considerably smaller doses of chlorpropamide will achieve concentrations of blood sulfonylurea and hypoglycemic action similar to that of tolbutamide.

This report is a summary of clinical studies during the last six months of 1958 of 53 patients with diabetes mellitus.

Material and Methods

Our clinical study of 53 diabetic patients consisted of three parts: trial of chlorpropamide in (1) 31 adult patients with stable diabetes, (2) four elderly patients with unstable diabetes, and (3) 18 young patients with diabetes.

Adult, stable diabetics. The 31 patients were selected for chlorpropamide therapy because they were candidates for tolbutamide therapy. They all had the so-called "stable" (onset at maturity) diabetes. They were between 32 and 81 years of age. Sixteen patients previously were well maintained on daily doses of from 10 to 52 units of insulin. Eight patients previously had received tolbutamide therapy up to 2 gm. daily, but in two, there was primary, and in six, secondary failure to respond to that therapy. Seven patients previously had followed a careful dietary program without obtaining adequate control of the hyperglycemia.

Adult, unstable diabetics. Four patients, from 30 to 64 years of age, had unstable diabetes. In them, minor changes in insulin dosage brought about rapid development of hyperglycemia and ketosis.

**Diabinese [1-(p-chlorobenzenesulfonyl) 3-propylurea] for this study was supplied through the courtesy of Pfizer Laboratories.*

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Young diabetics. Eighteen patients were young diabetics; the average age was 11 years, in a range of four to 17 years.

Results

Adult, stable diabetics. Of the 31 patients, the chlorpropamide treatment was successful in 28: primary failure occurred in two patients, and secondary failure in one patient. For 23 patients the control of diabetes was considered to be excellent; in those patients the blood sugar values were—fasting, less than 140 mg., and postprandially, less than 160 mg. per 100 ml. In five patients the results were good: there was no glycosuria, but the blood sugar values were higher than the above-mentioned values, although less than 190 mg. per 100 ml. fasting or postprandially. The average follow-up is more than three months, in a range of one to seven months. The average maintenance dosage of chlorpropamide was 285 mg. daily, in a range of 100 to 750 mg. per day.

Adult, unstable diabetics. Of the four adult patients with unstable diabetes, chlorpropamide therapy brought about a decrease in insulin requirement in one patient, and no change in the other three. One patient believed that he was better able to anticipate insulin reactions, although there was no objective change in their frequency or severity. In two patients the administration of chlorpropamide had to be stopped because of severe abdominal pain when the dose was greater than 1 gm. per day.

Young diabetics. In six of the 18 patients the insulin dosage could be decreased and satisfactory blood sugar values still could be maintained. In two patients, normal blood sugar content was maintained for eight weeks without any supplemental insulin. Insulin was then restarted because of increasing hyperglycemia in association with poor adherence to the diet. A third patient has maintained excellent control of glycemia for 22 weeks without supplemental insulin.

Comment

It is our experience that the same daily dosage of chlorpropamide must be maintained for from five to seven days in order to ascertain its full hypoglycemic effect. The therapeutic dosage of chlorpropamide usually decreases significantly with prolonged therapy during the course of weeks or months.

The only side effects were observed when the dosage of chlorpropamide was raised to more than 1 gm. per day. They consisted of abdominal pain, lethargy, somnolence, drowsiness, and ataxia. The neurologic symptoms resembled those of hypoglycemia, although the blood sugar values were not hypoglycemic.

Summary

Fifty-three patients with diabetes mellitus were treated with chlorpropamide (average daily dose of 285 mg.) for from one to seven months. The drug therapy was effective in 28 of 31 adult patients with stable diabetes. It was effective in a number of these patients in whom diabetes was not well controlled with tolbuta-

mide. Of four adult patients with unstable diabetes, one patient obtained a decrease in insulin requirement; the other three patients were unaffected by chlorpropamide therapy. With this drug therapy, temporary control was obtained in six of 18 young diabetic patients, and normal glycemia has been maintained in one of them without insulin administration. Severe side effects occurred only in the two patients who required more than 1 gm. of chlorpropamide daily.

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DEFICIENCIES IN STUART (PROWER) FACTOR, PLASMA THROMBOPLASTIN COMPONENT, PROTHROMBIN, AND FACTOR VII, DUE TO MALABSORPTION OF VITAMIN K

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HEMORRHAGIC phenomena occur in the malabsorption syndromes as an infrequent complication,[1-5] and are due to the "hypoprothrombinemia" that results from the impaired absorption of fat and the fat-soluble vitamin K from the bowel. More specifically, it has been demonstrated[6] that in vitamin K deficiency, regardless of its pathogenesis, not only is the amount of prothrombin decreased, but also the amounts of factor VII (stable factor, serum prothrombin conversion accelerator, proconvertin) and plasma thromboplastin component (PTC, Christmas factor).

This paper describes the blood coagulation defect in a patient[7] with idiopathic steatorrhea; in addition to deficiencies of prothrombin, factor VII, and PTC, there was also a deficiency of the Stuart[8] (Prower[9]) clotting factor.

Case History[1]

The patient, a 24-year-old white woman, was first examined on March 31, 1958, because of diarrhea and pedal edema of two years' duration, and severe anorexia of one month's duration. In June, 1956, and again in June and September, 1957, she received two units of whole blood because of anemia. After severe bleeding from the uterus and the urinary tract in December, 1957, she received six units of whole blood. For three weeks prior to examination she had persistent, frank, hematuria. Epistaxis and hemoptysis occurred occasionally, and she bruised easily. Excessive bleeding had not occurred in other members of the family.

On physical examination she weighed 115 pounds and appeared to be extremely malnourished. The tongue was red and atrophic. Numerous ecchymoses were present on both arms, and there were splinter hemorrhages beneath the fingernails. Moderate bilateral edema of the legs extended up to the thighs. Trousseau's sign was present. A tourniquet test was negative. The remainder of the physical examination gave normal findings.

Laboratory studies disclosed: blood hemoglobin content, 15.2 gm. per 100 ml.; hematocrit reading, 46 cc. per 100 cc.; white-cell count, 3,900 per cubic millimeter, with a normal differential count. There was macroscopic hematuria. Several stools contained occult blood (guaiac test) and large amounts of fat. A culture of the stool yielded no pathogens. The total serum protein content was 2.77 gm. per 100 ml.; serum

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albumin 0.43 gm., and serum globulin 2.34 gm. The serum potassium value was 3.4 mEq. per liter; serum calcium 5.0 mg. and serum phosphorus 2.9 mg. per 100 ml. The cephalin-cholesterol flocculation test was 2 plus in 24 hours. The results of an oral glucose tolerance test were consistent with malabsorption.

Roentgen examinations, of the chest, kidneys, ureters, bladder, and the upper and lower gastrointestinal tracts showed no abnormality. On roentgen examination of the small bowel there was evidence of fragmentation of the barium column consistent with a disordered motor pattern. The absorption curves of radioiodinated triolein and oleic acid indicated minimal absorption of both of these substances. A cystoscopic examination revealed blood emanating from the left ureteral orifice.

Preliminary coagulation studies disclosed a bleeding time (Ivy method) of three minutes, a platelet count (Rees-Ecker method) of 380,000 per cubic millimeter, a coagulation time (four-tube method) of 50 minutes (normal 10 to 20 minutes), and a normal clot retraction. The Quick one-stage prothrombin time ranged between 110 and 184 seconds. Circulating anticoagulants were not demonstrated by either the Conley[10] method or the Biggs and Macfarlane[11] method. There was 190 mg. per 100 ml. of fibrinogen (Fowell[12] method).

Material and Methods

All blood was drawn from antecubital veins by means of silicone-coated 20-gauge needles and silicone-coated glass syringes. Oxalated plasma was collected in plain glass tubes, and citrated plasma in silicone-coated tubes. Serum was obtained by allowing the blood to clot at 37° C. in uncoated glass tubes. Some specimens were immediately stored at −20° C. and were used, after thawing, as long as two months later.

Barium sulfate ($BaSO_4$) adsorbed plasma was prepared by adding 100 mg. of powdered $BaSO_4$ to each milliliter of plasma; the resulting mixture was incubated for 15 minutes at room temperature, and then was centrifuged. This $BaSO_4$ adsorbed plasma was used within a few hours. An eluate was prepared from the $BaSO_4$ used to adsorb normal plasma, by allowing the $BaSO_4$ to stand in a 5 per cent solution of trisodium citrate in 0.89 per cent saline solution for 15 minutes at 37° C. and then centrifuging the mixture. The supernatant solution represented a volume equal to that of the plasma adsorbed.

Plasma and serum from a patient deficient in factor VII were stored for two months at −20° C. The factor VII deficiency had been diagnosed according to the following criteria: (1) a prolonged one-stage prothrombin time that could be corrected by normal serum but not by $BaSO_4$ adsorbed normal plasma; (2) a normal thromboplastin generation test and Stypven time; (3) mutual correction with plasma deficient in Stuart factor; (4) a factor VII content of 8 per cent of normal. The PTC deficient serum used in the correction studies had been stored for four months at −20° C. Plasma from a patient with a deficiency of Stuart factor was obtained through the courtesy of John B. Graham, M.D., of Chapel Hill, North Carolina. The plasma had been lyophilized in a glass container and was reconstituted to its original volume by the addition of distilled water immediately before use.

In the Quick one-stage prothrombin test a commercial preparation of brain thromboplastin* was used. For correction studies the various combinations were mixed immediately prior to performing the test. Prothrombin was assayed by the two-stage method of Ware and Seegers,[13] using commercial preparations of factor V and the incubation mixture.† The thromboplastin generation test was carried out according to the method of Biggs and Douglas,[14] but with a platelet suspension that was two or three times more concentrated than they recommend. Factor V was assayed by the method of Alexander, Goldstein, and Landwehr,[15] modified by the addition of oxalated normal serum to the test mixture. Factor VII was assayed by the method of Owren and Aas.[16] Circulating anticoagulant activity was estimated, both in the one-stage prothrombin test and in the thromboplastin generation test, by using equal mixtures of normal and abnormal fractions preincubated for 15 minutes at 37° C. *Table 1* lists the relevant coagulation factors present in the various fractions of normal and of abnormal blood used.

Table 1.—*The relevant coagulation factors in the various fractions used in the correction studies.* ‡

	Normal plasma	$BaSO_4$ adsorbed normal plasma	Eluate from $BaSO_4$	Normal serum	Factor VII deficient plasma	Factor VII deficient serum	Stuart factor deficient plasma	Stuart factor deficient serum	PTC deficient serum
Prothrombin	+	−	+	−	+	−	+	−	−
Factor VII	+	−	+	+	−	−	+	+	+
Stuart factor	+	−	+	+	+	+	−	−	+
Factor V	+	+	−	−	+	−	+	−	−
Plasma thromboplastin component (PTC)	+	−	+	+	+	+	+	+	−
Antihemophiliac globulin	+	+	−	−	+	−	+	−	−

‡ + = present; − = absent.

Results

The clinical history and the preliminary coagulation studies, which included prolonged coagulation time and one-stage prothrombin time, suggested the presence of a coagulation defect of considerable severity. More detailed investigation of the individual clotting factors showed that a multiplicity of defects existed.

The results of the one-stage prothrombin tests are presented in *Table 2*, and those of the thromboplastin generation tests in *Table 3*.

**Bacto thromboplastin, manufactured by Difco Laboratories.*

†Manufactured by Difco Laboratories.

Table 2.—*Correction studies using the one-stage prothrombin test before and after the administration of 72 mg. of menadione sodium bisulfite*

From the patient		Normal				Plasma deficient in		Prothrombin time (Quick), sec.
Plasma, ml.	Serum, ml.	Plasma, ml.	Serum, ml.	$BaSO_4$ adsorbed plasma, ml.	$BaSO_4$ eluate, ml.	Factor VII, ml.	Stuart factor, ml.	
Blood drawn before vitamin K therapy								
0.1	—	—	—	—	—	—	—	184
—	—	0.1	—	—	—	—	—	14
0.09	—	0.01	—	—	—	—	—	21
0.08	—	0.02	—	—	—	—	—	19
0.05	—	0.05	—	—	—	—	—	14
0.05*	—	0.05*	—	—	—	—	—	15*
0.09	—	—	0.01	—	—	—	—	37
0.08	—	—	0.02	—	—	—	—	35
0.09	—	—	—	0.01	—	—	—	115
0.09	—	—	—	—	0.01	—	—	25
—	—	—	—	—	—	0.1	—	49
0.01	—	—	—	—	—	0.09	—	47
0.09	—	—	—	—	—	0.01†	—	40
0.05	—	—	—	—	—	0.05	—	31
—	—	0.1	—	—	—	0.09	—	20
—	—	—	—	—	—	—	0.1	130
—	0.1	—	—	—	—	—	0.09	130
—	—	—	0.1	—	—	—	0.09	20
—	—	0.1	—	—	—	—	0.09	30
Blood drawn after vitamin K therapy								
8 hours								
0.1	—	—	—	—	—	—	—	16
0.01	—	—	—	—	—	—	0.09	44
0.01	—	—	—	—	—	0.09	—	22
36 hours								
0.1	—	—	—	—	—	—	—	15
0.01	—	—	—	—	—	—	0.09	37
0.01	—	—	—	—	—	0.09	—	20
5 days								
0.1	—	—	—	—	—	—	—	14
0.01	—	—	—	—	—	—	0.09	27
0.01	—	—	—	—	—	0.09	—	20

* Mixture incubated at 37° C. for 15 minutes prior to performing the test.
† Serum.

‡ Should read: 0.01. See Errata, p. 92.

Table 3.—*Correction studies using the thromboplastin generation test before and after the administration of 72 mg. of menadione sodium bisulfite*

Variables in the incubation mixture	Incubation time, minutes					
	1	2	3	4	5	6
	Substrate clotting time, seconds					
Normal	55	14	8	8	9	9
Patient's $BaSO_4$ adsorbed plasma	55	20	10	8	8	9
Patient's serum	150	135	110	60	30	25
Patient's serum 90% + normal serum 10%	—	35	12	11	11	10
50% + 50%	32	11	10	9	9	9
50%* + 50%*	40	16	12	9	9	9
PTC deficient serum	60	25	25	28	30	31
Patient's serum 10% + PTC serum† 90%	60	25	25	25	25	25
50% + 50%	—	30	22	18	16	14
90% + 10%	90	60	20	18	16	15
Stuart factor deficient serum	105	98	80	60	40	26
Patient's serum 10% + Stuart serum‡ 90%	69	60	53	50	28	27
50% + 50%	32	14	13	13	13	13
90% + 10%	57	20	18	15	13	13
50% + {Stuart serum‡ 25%, PTC serum† 25%}	55	27	12	11	10	11
Patient's serum after injection of synthetic vitamin K—						
8 hours	72	16	12	11	13	13
5 days	42	8	7	8	10	10

*Preincubated for 15 minutes at 37° C.
†PTC deficient serum.
‡Stuart factor deficient serum.

In the preliminary studies the abnormality observed was so great as to suggest the presence of a circulating anticoagulant. However, by conventional methods no such anticoagulant was demonstrated. It was further shown that the abnormality neither in the one-stage prothrombin test nor in the thromboplastin generation test was due to circulating anticoagulant. Repeated assays of factor V throughout the investigation always showed values to be 100 per cent of normal. The patient's $BaSO_4$ adsorbed plasma acted normally in the thromboplastin gen-

eration test, indicating that there was no deficiency of antihemophiliac globulin; however, no specific assay of this factor was made.

When the amounts of fibrinogen and factor V are normal, and there is no circulating anticoagulant, a prolonged one-stage prothrombin time reflects a deficiency of prothrombin, factor VII, or Stuart factor.

It appeared that a deficiency of prothrombin existed when it was shown that the long one-stage prothrombin time was corrected to a greater extent by normal plasma, and by an eluate of $BaSO_4$ containing the factors adsorbed from normal plasma, than by normal serum and by $BaSO_4$ adsorbed plasma. Confirmation was obtained by the assay of prothrombin which was 8 per cent of normal.

The fact that normal serum partially corrected the patient's abnormal prothrombin time indicated that either factor VII or Stuart factor or both factors were reduced. A deficiency of factor VII was proved by the inability of the patient's plasma to correct the one-stage prothrombin time of plasma known to be deficient in factor VII. Specific assays of factor VII in the patient's plasma and serum were less than 5 per cent of normal.

Although the patient's plasma did not correct factor VII deficient plasma, factor VII deficient serum did partially correct the patient's abnormality in the one-stage prothrombin test. Thus, factor VII deficient serum appeared to contain some factor in which the patient was deficient. This factor proved to be Stuart factor when it was shown that the patient's serum was unable to correct a Stuart factor deficiency, either in the one-stage prothrombin test or in the thromboplastin generation test. Unfortunately, the quantity of plasma obtained from the patient prior to vitamin K therapy was insufficient to test whether or not the serum deficient in Stuart factor would correct the patient's abnormal one-stage prothrombin time by virtue of its factor VII content.

A deficiency of PTC, as well as of Stuart factor, existed in the patient's serum and was partly responsible for the abnormal results of the thromboplastin generation test. This was proved when the patient's serum failed to correct the abnormal thromboplastin generation of serum deficient in PTC. Both serum deficient in PTC (by virtue of its content of Stuart factor), and serum deficient in Stuart factor (by virtue of its PTC content) were able partially to correct the defect in the patient's serum. As one might expect, an equal mixture of sera deficient in PTC and in Stuart factor corrected the thromboplastin generation to a greater extent than did either alone, and to an extent comparable to the correction obtained with normal serum. These findings offered further confirmation of the dual deficiency of Stuart factor and of PTC.

Effect of the Injection of Vitamin K

All clinical evidence of hemorrhage rapidly disappeared after the patient

received a single intravenous injection of 72 mg. of menadione sodium bisulfite.* In vitro coagulation studies *(Tables 2-4)* showed a correspondingly rapid improvement. Within 24 hours after the injection, the factors previously deficient had returned to nearly normal values, and within five days to normal values. Stuart factor reappeared at the same rate as did the other factors. The patient has continued to receive vitamin K parenterally and her coagulation mechanism has remained normal.

Table 4.—*Factor VII and prothrombin values, and the one-stage prothrombin times, before and after the administration of 72 mg. of menadione sodium bisulfite*

After injection of vitamin K, hr.	One-stage prothrombin time, sec.	Factor VII assay, %	Prothrombin assay, %
0	184	5	8
8	16	35	30
36	15	100	60
56	14	100	100

Discussion

Douglas[7] has shown that PTC, as well as prothrombin and factor VII, is reduced in vitamin K deficiency. The results in our case confirm his findings and, in addition, show a significant reduction in Stuart factor. Since the concentration of this factor is low in the plasma of patients who have received coumarin drugs,[8] one would expect it to be reduced in vitamin K deficiency. However, there is no previous report of deficiency of Stuart factor as the result of the malabsorption of vitamin K.

It is possible that yet other factors were deficient in our patient. Thus, plasma thromboplastin antecedent (PTA) was not specifically investigated; however, the findings do not suggest that a deficiency of this factor existed. In investigating multiple coagulation defects, one is largely limited by the available number of known abnormal plasmas and methods of specific assay. Despite these limitations, a deficiency often can be inferred by cross-correction studies. In this case, for instance, whereas the patient's serum did not correct the long one-stage prothrombin time of plasma deficient in factor VII, serum deficient in factor VII did partially correct the patient's prolonged one-stage prothrombin time. These findings suggested that besides factor VII, the patient's serum was deficient in another factor—subsequently shown to be Stuart factor.

**Hykinone (menadione sodium bisulfite), Abbott Laboratories.*

There is little doubt that the various coagulation deficiencies present in our patient were due to the malabsorption of vitamin K. The principal evidence for this conclusion is the existence of a disease, idiopathic steatorrhea, in which poor absorption of vitamin K might be expected, and the rapid favorable response to the administration of synthetic vitamin K. Such rapid improvement following administration of vitamin K is well documented. As was expected, Stuart factor and the other factors returned to normal almost simultaneously. The four factors involved, namely, Stuart factor, PTC, prothrombin, and factor VII, have several properties in common: they are dependent on vitamin K for their production, depressed by coumarin drugs,[8, 17, 18] and adsorbed from plasma by inorganic precipitates such as $BaSO_4$. Single deficiencies of these factors do occur, mainly as hereditary defects. However, these factors appear to be more closely related than might be suggested by their actions in different stages of blood coagulation.

Summary

A case of idiopathic steatorrhea with severe hemorrhagic manifestations due to malabsorption of vitamin K is described. Detailed coagulation studies disclosed a deficiency of Stuart factor, in addition to deficiencies of plasma thromboplastin component, prothrombin and factor VII. The coagulation mechanism was rapidly restored to normal by the intravenous administration of synthetic vitamin K.

Acknowledgment

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Addendum

Since submitting this paper for publication, the paper by T. H. Spaet and Mona Kropatkin entitled, *Studies on "Prothrombin Derivatives" in Vitamin K Deficiency,* has been published in the A.M.A. Archives of Internal Medicine, volume 102, pages 558-561, October, 1958. The authors report a case of intestinal malabsorption resulting in vitamin K deficiency, associated with deficiencies of Stuart factor, factor VII, and prothrombin.

HIGH ARTERIAL PRESSURE AS A PRIMARY CAUSE OF HYPERTENSIVE VASCULAR LESIONS*

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and
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Division of Research

GULL and Sutton[1] in 1872 defined the concept of the primacy of "arterio-capillary fibrosis" as the cause of hypertension in the "forbid state called chronic Bright's disease with contracted kidney." They based their conclusions primarily on studies at necropsy. Mahomed,[2] in 1879, reported the opposite conclusion. He was primarily a clinician, and was one of the first to measure arterial pressure and to correlate it with clinicopathologic changes. He[3] considered that there were "three stages of chronic Bright's disease: first, the *functional stage,* which is limited to the condition of high arterial pressure without organic changes in either the vascular system or the kidneys; second, the *chronic Bright's disease without nephritis,* the stage of organic changes in the vascular system and in the kidney (for which, if thought desirable, the term 'arterio-capillary fibrosis' might be employed); third, *chronic Bright's disease with nephritis,* the natural, but by no means the invariable, termination of the disease." Unfortunately, Mahomed died while still a young man, and was thus prevented from convincing the medical public by further demonstrations of the natural history of the disease; the authority of the older, presumably wiser, men prevailed.

The demonstration by Goldblatt, Lynch, Hanzal, and Summerville,[4] in 1934, that in dogs, partial occlusion of the main renal artery could cause hypertension of varying severity, seemed to support the view that primary nephrosclerosis, if not diffuse "arterio-capillary fibrosis," might be the true event in hypertension. This concept received further support in 1937 from the observations of Moritz and Oldt[5] that people who died of complications of hypertension, consistently showed signs of nephrosclerosis, and that, whereas in previously normotensive subjects, extrarenal arteriolar lesions were frequently present, renal arteriolar lesions were conspicuously absent. More than 25 years of further clinical, experimental, and pathologic studies of hypertension have not resolved the issue.

The experiments of Wilson and Byrom,[6, 7] Wilson,[8] Floyer,[9] and Selye and Stone[10] represent a large body of evidence that, in rats, hypertension will cause, and relative normotension or hypotension will tend to prevent, nephrosclerotic

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lesions. These data concur in supporting the thesis that high arterial pressure per se is a primary, if not the only significant, factor in the pathogenesis of these lesions. The design of these experiments unfortunately was such that the associations observed for the most part were definable only in qualitative rather than in quantitative terms. A direct approach to the problem by forced intraarterial injections was made by Byrom and Dodson,[11] by us,[12] and by Schaffenburg and Goldblatt,[13] but with discordant results. These are considered next.

Quantitative associations have been reported[14] between the degree of arterial hypertension and the severity of hypertensive vascular disease in small groups of rats with hormonal (desoxycorticosterone) hypertension, which were treated with hydralazine hydrochloride, or reserpine, or with both agents. Koletsky[15] controverted these associations in rats that had renal hypertension; he injected dibenamine, a relatively ineffective antihypertensive drug. More recently, a quantitative association of high arterial pressure and arterial lesions has been defined[16] from results in rats with hypertension due to partial renal infarction, some of which were treated with hydralazine hydrochloride. In those experiments we demonstrated the presence of a specific hypersusceptibility of the renal vascular bed to the development of nephrosclerosis, even when arterial pressures were not conspicuously or continually elevated.

Some investigators still are not convinced of the association between elevated pressure and lesions, or of the primacy of high pressure in causing lesions. They believe that other factors, as for example the presence[17] or absence[18] of intact renal tissue, partly or wholly determine the occurence of hypertensive vascular disease, particularly that which is acute, fulminant, and severely destructive. Perera[19] believes that he has demonstrated clinically a condition of "hypertensive disease without hypertension." The controversy spans more than 80 years, and has followed various trends—often accompanied by more conviction and acerbity than evidence.

The data that we now report, together with the previous experience of Corcoran, Dustan, and Page,[20] and with observations on the course of severe human hypertension as affected by long-term treatment with effective antihypertensive drugs[21] serve to convince us of an association between elevation of pressure and lesions, and of the primacy of high arterial pressure in causing lesions in various hypertensive states. This relationship does not preclude the participation of other factors, such as the apparent generalized sensitization to lesions produced by nephrectomy, whether or not there are subsequent vividialyses,[17, 22] administration of sodium-rich electrolyte solutions [23] or injections of renin.[24]

Effects of Increased Arterial Pressure

As noted above, results of direct experiments have not been concordant. Byrom and Dodson[11] reported that in rats, forced, manual, intracarotid injections of 2 ml. of saline solution, repeated from 10 to 15 times, caused, at the time of injection, widespread focal spasms of renal arteries, as evidenced by blanching of

the kidney. A few days later at necropsy they observed focal arterial necrosis, especially in the renal vascular bed. Arterial pressure, registered by a mercury manometer, increased as much as from 80 to 90 mm. of Hg during the injections. Using a mechanical device* we[12] confirmed these findings. They were briefly presented earlier, and are described here in detail.

The injection apparatus consisted of a 50-ml. syringe enclosed partly in an air-tight glass cylinder connected by a regulating valve with a container of compressed nitrogen. It was possible to regulate accurately the pressure in the air chamber and, therefore, the flow of Ringer's solution from the syringe. A three-way stopcock permitted easy filling or evacuation of the Ringer's solution through a No. 22 needle inserted into the carotid artery. The critical pressure was 2 kg. per square centimeter at a flow rate of 240 ml. per minute: with a higher rate, fatal hemorrhages occurred in the aorta. Since a mercury manometer was ill-adapted to the exact measuring of arterial pressure at the time of injection, we used a capacitance manometer that was cannulated to the femoral artery. Our mechanical device yielded equal, reproducible increases in pressure.

Immediately at the time of each injection there was a rapid rise in arterial pressure *(Fig. 1)*. Since the rise was not maintained throughout the injection, we

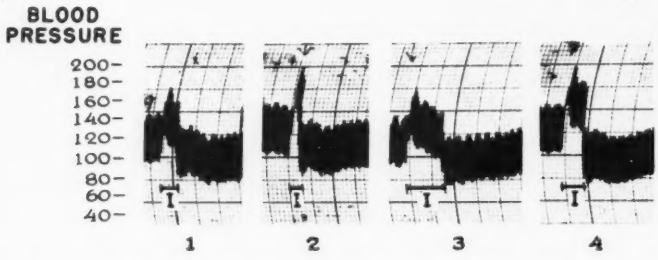
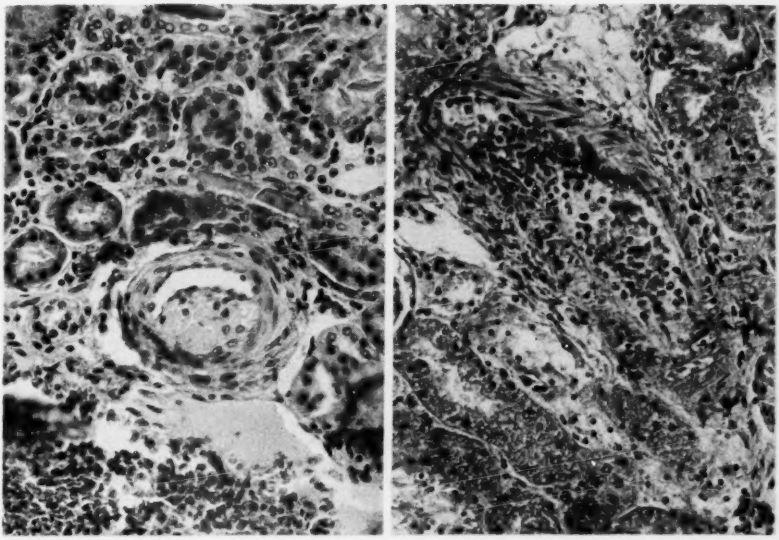


Fig. 1. Recorded graph of effects of intracarotid injections on femoral arterial pressure. Injections of 2.5 ml. of Ringer's solution under pressures of (1) 0.7 kg., and (2) 2 kg. per square centimeter. Injections of 5 ml. of Ringer's solution under pressures of (3) 0.7 kg., and (4) 2 kg. per square centimeter. Interval I represents duration of injection. *Published through the courtesy of the Revue Canadienne de Biologie.*[12]

believed it to be more important to increase the number rather than the volume of the injections. We injected doses of from 2.5 ml. to 5 ml. every two minutes up to a total volume of 80 ml. Rats were sacrificed from 8 hours to one week after each series of injections. Blood pressure of some as recorded by plethysmography of the tail was regularly increased up to 180 mm. of Hg from a base line of about 100 mm. of Hg during the succeeding five days, followed by an abrupt decline that was fatal.

**The mechanical device was constructed by Mr. Frederick Olmsted of the Division of Research.*

The lesions were restricted to the kidneys; they consisted of hemorrhages, excessive distention of arteries and arterioles, edema of the intima, which resulted in partial obliteration of the lumen, and focal fibrinoid necrosis of the muscularis *(Fig. 2, A and B)*. There was no evidence that these injections caused lesions of



A B

Fig. 2. Photomicrographs of sections of renal tissue after intracarotid forced injections. A, Arteriole, with evidence of distention and focal swelling of the endothelium, hemorrhage, and edema of interstitial tissues. Masson's trichrome stain; magnification x 200. B, Wall of an artery with evidence of hemorrhages and fibrinoid necrosis, also necrosis of the tubules. Masson's trichrome stain; magnification x 200. *Published through the courtesy of the Revue Canadienne de Biologie.*[12]

splanchnic arteritis, such as occur in rats with severe hypertension. These observations are essentially in accordance with those of Byrom and Dodson,[11] but differ from the more recent ones by Schaffenburg and Goldblatt,[13] who, like Byrom and Dodson injected fluid manually in amounts of 2 ml., repeated at intervals of one minute, up to a total volume of 30 ml. They reported maximum rises in arterial pressure to 194 mm. of Hg above the base, which are considerably higher than those that we observed. However, since their measurements were made with a mercury manometer connected to the aorta, the high values may reflect in part the momentum of the mercury column. Thus, although the conditions of their experiments are similar to those of Byrom and Dodson[11] allowing for differences in manually controlled injections, Schaffenburg and Goldblatt[13] did not detect any pathologic vascular changes.

Effects of Lowered Arterial Pressure

A clear demonstration of the relationship between pressure and vascular disease has been provided by our results with antihypertensive agents in rats with experimentally produced renal infarcts. Renal infarction was produced in one kidney by the method of Loomis,[25] and was associated with contralateral nephrectomy. Sham-operated, uninephrectomized rats served as control animals. Hydralazine hydrochloride* (hereinafter termed "hydralazine") was selected as a potent hypotensive agent. A series of preliminary experiments established that it would cause sustained hypotension when given in drinking water. That a maximally effective dose was thus given was confirmed by the absence of a further decrease in arterial pressure when, after seven days of oral treatment, a test dose of hydralazine was given by gavage.

Two series of experiments were performed. In Series I, we were concerned with the effects of hydralazine-induced control of hypertension on the acute lesions that developed during the first seven to 15 days after operation; and in Series II, on the effects over periods of one and two months, including the effects of one month of hydralazine treatment on lesions that had developed in the absence of treatment during the first month.

Series I. Effects of hydralazine on acute vascular lesions (Table 1). Particular attention was paid to changes in the extrarenal vascular bed, because of the possibility

Table 1.—*Effects of hydralazine during acute renal hypertension (Series I)*

Group	No. of rats	Treatment	Duration of experiment, days	Percentage with extrarenal vascular disease, %	Heart wt. as percentage of body wt., %
1	14	0	7	66	.34
2	22	+	7	18	.32 (.28—.38)
3	22	0	15	68	.30 (.25—.39)
4	21	+†	15	57	.34 (.28—.40)
5	10	0‡	7	0	.26 (.23—.28)

† Hydralazine started on the seventh day.

‡ Sham-operated control.

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**Apresoline (hydralazine) hydrochloride was generously provided by Ciba Pharmaceutical Products Inc.*

of confusing renal lesions consequent to infarction with those attributable to hypertensive disease. In the absence of treatment, extrarenal vascular lesions, primarily splanchnic, were present in about two thirds of the animals. During continuous treatment with hydralazine from the time of operation, the arterial pressure was maintained within normal limits in most animals, and the incidence of extrarenal lesions decreased from 66 per cent to 18 per cent. No lesions were found in the uninephrectomized sham-operated control animals; however, in these experiments, as in those of Series II, the administration of hydralazine did not prevent the development of myocardial hypertrophy.

Series II. Effects of hydralazine on chronic vascular lesions. In these experiments, as in those of Series I, hydralazine administered orally prevented the otherwise expected rise of arterial pressure for periods as long as two months *(Fig. 3)*.

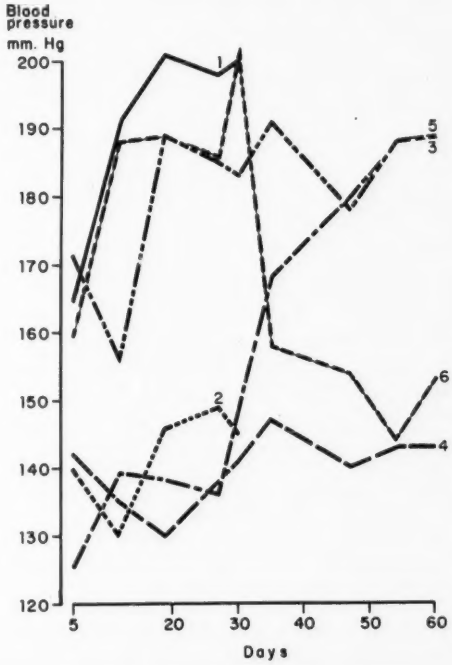

Fig. 3. Graph of changes in blood pressure in the six groups of animals listed in Table 2.

When, at the end of one month of treatment, the administration of hydralazine was discontinued, arterial pressures rose promptly to hypertensive levels, and lesions, which had been inhibited, developed in florid form by the end of the second month.

Animals continuously under treatment for either one or two months had a smaller number of lesions as compared with untreated hypertensive control animals *(Table 2)*. Gross splanchnic arteritis was present only in the untreated (one or

Table 2.—*Effects of hydralazine during chronic renal hypertension (Series II)*

Group	No. of rats	Treatment	Duration of experiment, mos.	Mortality	Percentage with extrarenal vascular disease, %	Heart wt. as percentage of body wt., %	Gross arteritis
1	10	0	1	4	100	.43 (.32—.64)	+
2	10	+	1	1	22	.32 (.33—.43)	0
3	10	0	2	2	85	.36 (.27—.49)	+
4	8	+	2	1	20	.37 (.33—.43)	0
5	10	+*	2	2†	70	.35 (.28—.46)	+
6	10	+‡	2	3†	90	.34 (.31- .41)	+

*Treatment was terminated on the thirtieth day and animals sacrificed one month later.

†Mortality occurred after operation (group 5), or before initiation (group 6) of treatment.

‡Treatment was initiated on the thirtieth day and animals were sacrificed one month later.

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two months) hypertensive control animals, and in animals that had been treated for one month and then left untreated during the second month *(Fig. 4, A and B)*. Healed lesions occurred in animals allowed to be hypertensive for the first month and treated during the second month *(Fig. 4, C)*.

Throughout, as in the short-term experiments (Series I), there was a strong association between blood pressure, as measured by plethysmography of the tail, and the presence, absence, state of regression, or activity of the extrarenal vascular lesions.

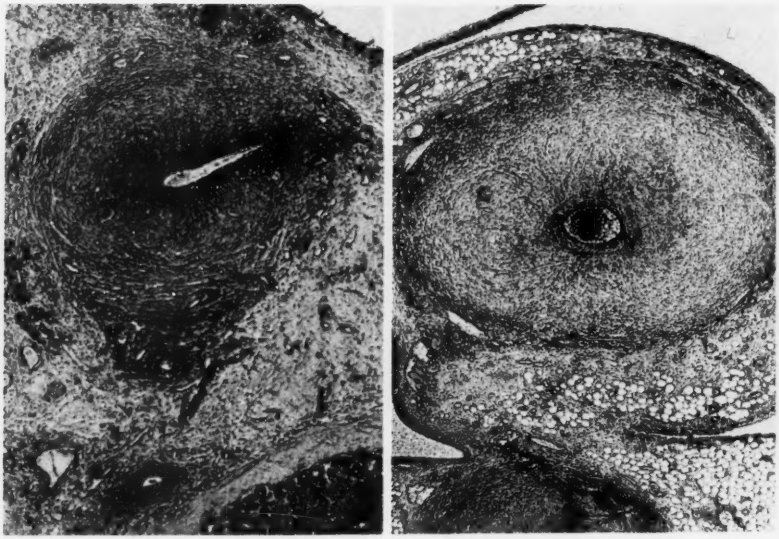
The sensitivity of the renal vascular bed was demonstrated by the presence of unexpected lesions consisting of progressive damage to large arterioles and small arteries in the kidneys of the animals maintained under continuous treatment, with blood pressures with the range of normal *(Fig. 4, D)*. Possibly some of these may have been transiently hypertensive at some time during treatment. The results of our direct injections suggest that only from 20 to 30 such episodes, each lasting less than a minute, might result in renal lesions. Such transient episodes could be easily missed in the course of biweekly determinations of arterial pressure by plethysmography. As in Series I, cardiac hypertrophy was not prevented by such treatment. In this respect the experience is similar to that of the clinical treatment of hypertension with hydralazine.[26] Possibly this may reflect the tendency of hydralazine to cause tachycardia. Some states of tachycardia, as for example hyperthyroidism, are associated with cardiac enlargement.

Neurogenic Hypertension

One disturbing inconsistency in the association between hypertension and arterial lesions is the fact that most workers have not seen such lesions in the course of neurogenic hypertension due to buffer nerve resection in dogs.[27-29] However, lesions have been described by Dammin, Goldman, Schroeder, and Pace,[30] in dogs that were made hypertensive by bilateral buffer nerve section and were then maintained for periods as long as three and one-half years. The lesions occurred primarily in the glomerular basement membranes. They do not seem to us to be characteristic of diffuse nephrosclerosis. Furthermore, it should be remembered that dogs with moderate degrees of renal hypertension may be maintained for periods as long as six years without the occurrence of recognizable renal vascular lesions in the kidney contralateral to that causing the hypertension.[17] Thus, it appears that dogs are more resistant to the nephrosclerotic effects of arterial hypertension than are rats. Therefore, induction of chronic, neurogenic hypertension in rats should represent a better approach to this problem. From our experience with other forms of hypertension in rats one might expect it to be associated with nephrosclerosis and with the splanchnic vascular disease characteristic of hypertension in this species.

Summary and Conclusions

The controversy as to the primacy of high arterial pressure in the pathogenesis of hypertensive arterial disease has continued for 80 years and has not been resolved by the past 25 years of study of various experimental types of hypertension. A body of evidence indicates that factors other than pressure participate in the pathogenesis of certain acute necrotizing lesions. However, recent clinical remissions in patients with severe hypertensive disease who were given antihypertensive drugs, indicate that high arterial pressure must be a primary factor in the causation of hypertensive vascular disease.

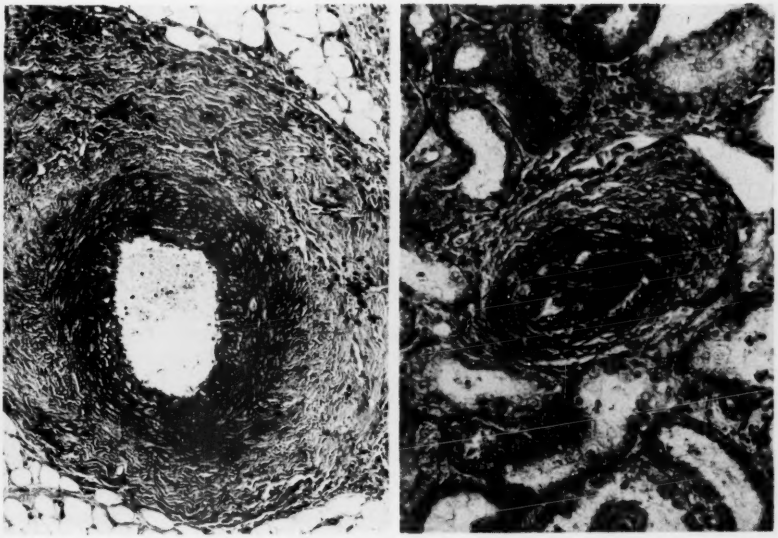


A B

Fig. 4. A, Photomicrograph of a section of an acute arteritic lesion in a rat with renal infarction maintained without treatment for one month. Periodic acid—Schiff stain; magnification x 45. *Published through the courtesy of The American Journal of Pathology.*[16] B, Photomicrograph of section of acute arteritic lesion similar to the one of A in a rat with renal infarction treated with hydralazine during the first month, then maintained without treatment during the second month. Periodic acid—Schiff stain; magnification x 40.

This clinical view has experimental support: (1) in rats, forced, brief rises of arterial pressure evoke acute fibrinoid necrosis of renal vessels; (2) rats with renal infarction, given hydralazine as an antihypertensive agent, demonstrate a close association between levels of pressure and the incidence, degree, state of healing, or activity of extrarenal, hypertensive, vascular lesions. Renal vascular lesions were found in treated, apparently normotensive animals, but these, in view of the lesions caused by forced rises of arterial pressure, may be attributed to repeated, brief, undetected "escapes" from the effect of hydralazine.

The absence of hypertensive vascular disease in dogs with neurogenic hypertension is noted; attention is drawn to the dog's resistance to chronic hypertensive vascular disease, and it is suggested that experiments in the rat may resolve this



C D

Fig. 4. C, Photomicrograph of a section of a healed lesion of arteritis from a rat with renal infarction, untreated during the first month then treated with hydralazine during the second month. It can be assumed that at the end of the first month this artery was similar to the one indicated in Fig. 4 A. The central dark core represents the limits of the original normal artery; it is surrounded by sclerosed tissue in which dark spots representing pigments of blood can be distinguished. Periodic acid—Schiff stain; magnification x 100. *Published through the courtesy of The American Journal of Pathology.*[16] D, Photomicrograph of a section of a small renal artery with evidence of progressive occlusion due to deposition of periodic acid—Schiff positive material. This section is from a rat with renal infarction, which was treated with hydralazine for two months. There were no extrarenal vascular lesions. Periodic acid—Schiff stain; magnification x 220. *Published through the courtesy of The American Journal of Pathology.*[16]

single inconsistency in the otherwise rather uniform causal association between high arterial pressure and hypertensive vascular disease.

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HAND-SCHÜLLER-CHRISTIAN DISEASE WITH UNUSUAL ROENTGENOGRAPHIC FINDINGS OCCURRING IN AN ADULT

Report of a Case

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and

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Department of Anatomic Pathology

THE usual roentgenographic manifestions of Hand-Schüller-Christian disease consist of a few radiolucent defects of moderate-to-large size in the calvaria and sometimes in the peripheral bones. These lesions most often occur in children, rarely in adults. Our purpose is to report a case of Hand-Schüller-Christian disease in an adult with unusually extensive involvement of the long bones in addition to the common roentgenographic findings.

Case Report

A 40-year-old white man was first examined at the Cleveland Clinic in March, 1954, because of excessive thirst (consuming two gallons of water daily), frequency of urination, and loss of libido. On physical examination the only abnormal finding was small testes. Roentgenograms of the skull were normal. The chest roentgenogram showed evidence of a finely nodular infiltrate, particularly in the upper lobes, suggestive of sarcoidosis; however, the Nickerson-Kveim test was negative. The clinical impression was that of pituitary insufficiency with diabetes insipidus.

Two years later, in 1956, he was re-examined because of multiple symptoms, including the recurrence of those of pituitary insufficiency, generalized weakness, and pain in the ankles. Roentgen examination at that time revealed no change in the appearance of the chest. Roentgenograms of the skull again demonstrated evidence of a normal sella turcica, but there were two radiolucent areas in the parietal region. Roentgenograms of the right ankle gave evidence of a pathologic fracture of the talus with collapse, and obvious bony defects about the ankle *(Fig. 1)*. Bone survey studies evidenced diffuse involvement of the skeleton, with the exception of the spine, by multiple, small, rounded defects *(Figs. 2 and 3)*. The serum calcium content was 9.0 mg., and the serum phosphorus content 5.5 mg. per 100 ml. The alkaline phosphatase concentration was normal.

Because of the peculiar roentgenographic findings in the long bones, a biopsy of the tibia was performed. The tissue that was removed was lemon yellow, soft, and homogeneous, with a few intermingled bony spicules. Microscopic examination revealed replacement of the marrow by various abnormal cells, large numbers of which had an abundant, definitely vacuolated cytoplasm and relatively small nuclei. These cells were

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intermingled with multinucleated giant cells that had the same type of vacuolated cytoplasm *(Fig. 4)*. Large numbers of lymphocytes and a few eosinophils were present. Sudan IV stains of frozen sections faintly colored the cells having vacuolated cytoplasm *(Fig. 5)*. Examination with polarized light demonstrated that the intracytoplasmic sudanophilic material was anisotropic; the Schultz stain was positive for cholesterol. A correlation of these pathologic findings with the clinical features resulted in the diagnosis of Hand Schüller-Christian disease.

Fig. 1. Roentgenogram of the right ankle with evidence of a pathologic fracture of the talus and, in addition, multiple small radiolucent defects in the tibia, the fibula, and the bones of the foot.

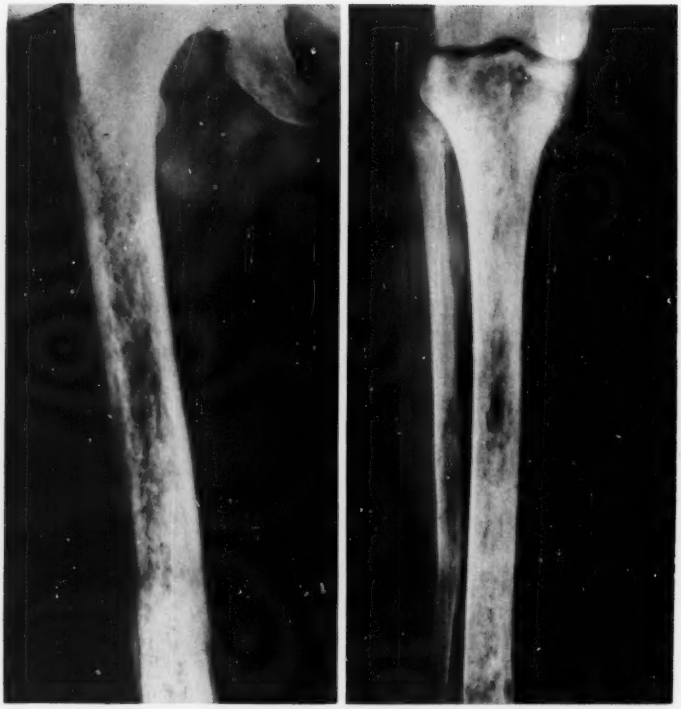

Fig. 2. Roentgenograms of the femur and of the tibia and fibula, with evidence of numerous small radiolucent defects.

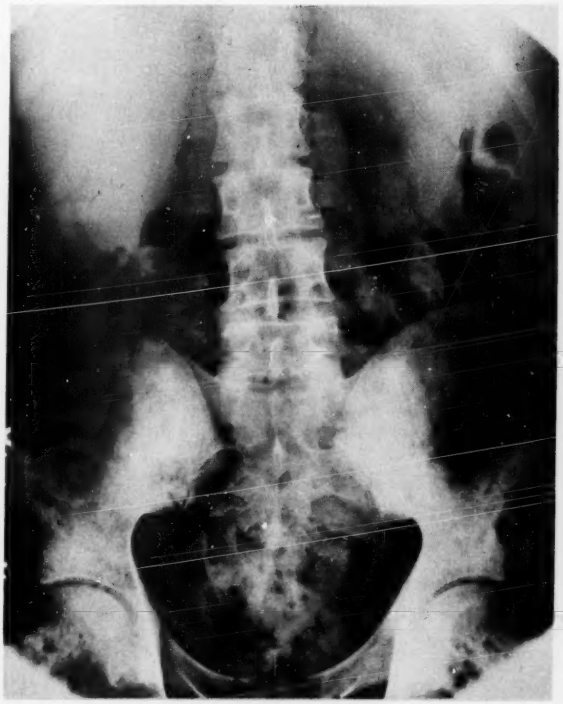

Fig. 3. Roentgenogram of the pelvis showing evidence of numerous small islands of osseous loss similar to those observed in the extremities. The vertebrae apparently are not involved.

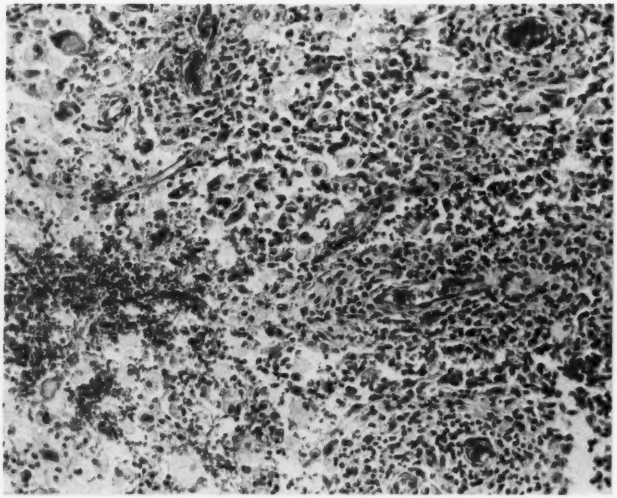

Fig. 4. Photomicrograph of a routinely processed histologic section of tissue from the tibia, with evidence of abnormal tissue formed by cells with an abundant, finely vacuolated cytoplasm, and single, round, vesicular nuclei, multinucleate giant cells, and lymphocytes. Hematoxylin-eosin — methylene blue stain; magnification x 140.

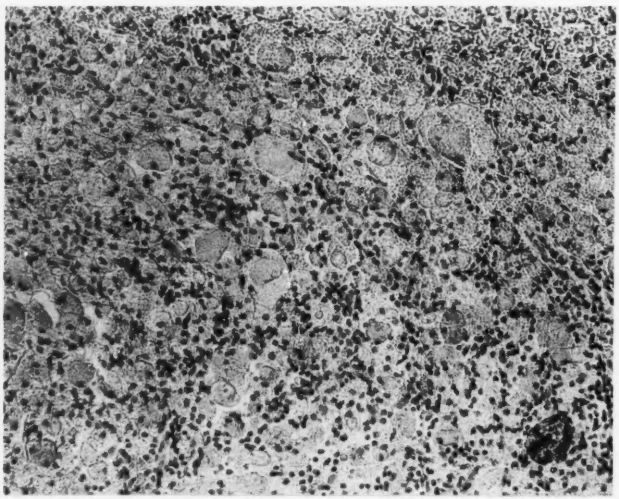

Fig. 5. Photomicrograph of a frozen section of tissue from the tibia, with evidence of slight sudanophilia. Sudan IV stain; magnification x 140.

MILKMAN'S SYNDROME

A Brief Review of the Literature and Report of a Case

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and
THOMAS F. MEANEY, M.D.†
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MILKMAN'S syndrome is a form of osteomalacia characterized radiologically by radiolucent zones or bands of decalcification traversing otherwise normal-appearing bone, usually at right angles to the long axis of the bone. These ribbon-like bands have been called "pseudofractures," "Looser's lines," "Umbauzonen," "Umbaufrakturen," "multiple spontaneous idiopathic symmetrical fractures," "osteoporosis melolytica," "insufficiency fractures," and "spontaneous fractures."

History

Mention of this phenomenon dates back to 1881, when Parker[1] reported the postmortem presence of spontaneous bilateral fractures in several ribs of a 12-month-old child with rachitic deformities. Feiss,[2] in 1905, described the condition of a four-year-old rachitic child with bilateral multiple spontaneous fracture-like zones, but with no displacement of fragments or other evidence of true fractures. In 1911, Hagemann and Eringhaus were reported by Fromme[3] to have found peculiar spontaneous fractures in a patient in the late stage of rickets.

In 1920, Looser[4] described radiolucent zones observed in his study of cases of starvation in Central Europe after World War I. He originally described the lesions as "transverse or oblique fissures or band-like . . . radiolucencies which divide the bone into two pieces but are not roentgenologically or clinically actual fractures." In 1930 and in 1934, Milkman[5, 6] described this syndrome as a separate disease entity. He related his work to that of Looser, but since Milkman's first reports, this condition has become associated with his name and, to date, reports of more than 60 cases of Milkman's syndrome have been published.

Etiopathogenesis

The true nature of Milkman's syndrome has been the subject of controversy. Milkman himself considered the cause unknown. Camp and McCullough[7] reported finding bony lesions similar to those in Milkman's syndrome in a number of conditions including Paget's disease, congenital syphilis, Von Recklinghausen's

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disease, and march fractures. However, those lesions do not fit the true definition of Looser's lines; that is, they do not occur in otherwise normal-appearing bone, and their distribution is not symmetric. Albright, Burnett, Parson, Reifenstein, and Roos[8] in 1946 argued that true multiple symmetric pseudofractures occurred only in osteomalacia, and this thesis has generally become the accepted opinion today. In all of the proved cases of Milkman's syndrome studied by Albright and his associates the chemical determinations of the serum were consistent with those obtained in cases of osteomalacia, that is, there were normal or low serum calcium, normal or low serum phosphorus, and high serum alkaline phosphatase values. The typical values in Milkman's syndrome are normal for serum calcium, low for serum phosphorus, and high for serum alkaline phosphatase.

The etiologic classification of osteomalacia published by Albright and his associates[8] is reproduced in *Table 1*. They recorded cases of Milkman's syndrome

Table 1.—*Etiologies of osteomalacia met in the United States**

Classification:

A) Vitamin D lack;
   a) "Simple" vitamin D lack
   b) Resistance to vitamin D
   c) Steatorrhea

B) Renal Acidosis;
   a) Tubular insufficiency-without-glomerular-insufficiency
   b) Fanconi Syndrome

C) Idiopathic Hypercalcuria

D) Hyperparathyroidism with Osteitis Fibrosa Generalisata during transitional stage following removal of parathyroid tumor.

**Reproduced through the courtesy of Medicine.*[8]

due to each of the etiologic factors mentioned, with the exception of simple vitamin D deficiency, and concluded that: ". . . it may be stated that ribbon-like zones of decalcification which occur in otherwise normal-appearing bone, which last months or years without regressing, and which exhibit a marked tendency to be symmetrical, occur only in osteomalacia or rickets." Subsequently, Winston and Pendergrass[9] reported a case that may well have been due to simple lack of vitamin D. The course of the disease in their patient was characterized by remissions and exacerbations; the remissions were directly correlated with the administration of vitamin D and calcium.

Many theories have been advanced as to the exact mechanism of production of the pseudofractures. Among these are: the presence of infection and sympathetic

bone disease; affection of the periosteum and the marrow; hormonal influence; and disease of the central nervous system. None of these conditions satisfactorily explains the symmetric distribution of the pseudofractures. Looser[4] explained the lesions on the basis of excessive strain, both muscular and postural, on an already weakened skeletal structure. Milkman[6] suggested the possibility of a control mechanism in the nervous system, which regulates small localized trophic changes. This control could be directed by the blood supply, and would explain the increased vascularity in the involved areas. Le May and Blunt[10] could not account for pseudofractures at bony regions not directly associated with strain, and advanced the concept of repeated and long-sustained trauma from the pressure of adjacent arteries at certain bony sites. In four proved cases of Milkman's syndrome they were able to correlate the locations of pseudofractures with vascular dissection at three (unrelated) necropsies. In many instances, arteries lay in close proximity to bone at points where pseudofractures were roentgenographically demonstrated in their four patients. From this study they postulated that long-standing pressure and pulsation of arteries caused small erosive defects in the osteomalacic bone, resulting in the formation of uncalcified osteoid. In further support of this theory are the findings of Steinbach, Kolb, and Gilfillan,[11] who made arteriographic studies of patients with Milkman's syndrome. Their studies showed the presence of arteries immediately adjacent to the sites of pseudofractures.

Cohen[12] demonstrated two cases of pseudofractures in ribs of patients who had extraperiosteal Ivalon packs when undergoing collapse therapy of the lung for pulmonary tuberculosis. He reasoned that the lesions could have been caused by trophic changes due to the removal of the periosteum and the nerve supply or the blood supply.

Radiologic Features

The radiologic features of Milkman's syndrome are pathognomonic, and consist of pseudofractures or Looser's lines that range from 1 mm. to 1 cm. or more in width. They are multiple, usually symmetrically distributed, and may occur both in tubular and in flat bones. There is some disagreement as to the bony sites most commonly involved, but lesions have been reported as occurring in almost all bones of the body. Some of the more common sites are the ribs, the coracoid process and the border of the scapula, the pelvis (particularly the ischial and pubic rami), the femur, the tibia, the fibula, the radius, the ulna, the clavicle, and the metatarsal and metacarpal bones. More rarely involved are the humerus, the phalanges, the carpal and tarsal bones, and the ilium. The pseudofractures often appear at identically corresponding sites and in equal numbers in involved paired bones. The lesions are first identified on roentgenograms as small punctate radiolucent areas that may appear to be placed centrally in the region of the spongiosa or laterally in the cortex, depending on the projection of the radiograph. As they progress, the lesions gradually encircle the entire cortex, usually at right angles to the long axis of the bone, and it appears as though the bones

were actually erased at those sites. Rarely there may be oblique or Z-shaped fissures.

The margins of the radiolucent bands are well defined, mildly sclerotic, and slightly jagged and uneven *(Figs. 1 and 2)*. There is no discontinuity or distortion in the line of the bone, and no evidence of the formation of callus. These are features that distinguish the lines from true fractures. However, these areas may proceed to fracture with displacement of fragments if they are subjected to sufficient stress.

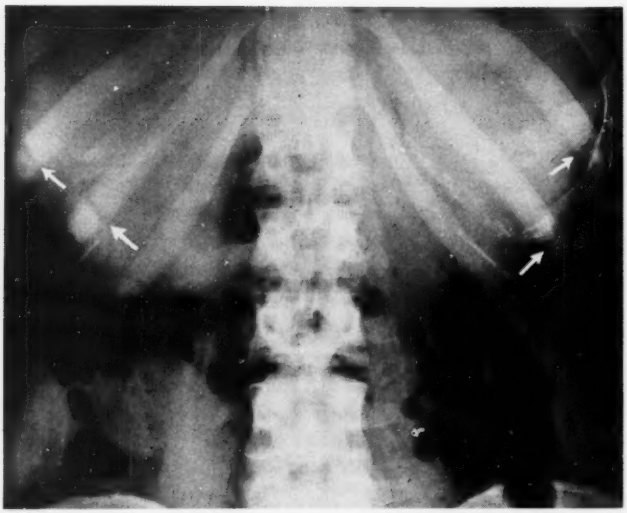

Fig. 1. Roentgenogram showing bilateral Looser's lines (arrows) in the tenth and eleventh ribs. There is no evidence of displacement of fragments.

Clinically, point tenderness often occurs over the bony lesions, and this evidence usually precedes the actual changes visible on roentgenograms. As a part of this syndrome, Milkman[5, 6] described a symptom-complex consisting of lumbosacral pain, point tenderness at various sites, difficulty in raising the leg, waddling gait, and generalized weakness.

Case Report

A 26-year-old, married, white woman was first examined on July 18, 1958. She had been well until two years before, when, during her fifth month of pregnancy, she first noted aching pain in the feet and the knees. Subsequently the pain increased and involved also the lumbar region, the hands, and the rib cage. This pain has persisted to

Fig. 2. Roentgenogram of the tenth and eleventh ribs, showing Looser's lines in detail (arrows). Note the jagged and slightly sclerotic margins of the pseudofractures. There is no evidence of formation of callus.

the time of writing this report. She stated that there had been no redness or swelling of the joints.

At the physical examination, pressure on the ribs elicited pain, and there was point tenderness over the left fourth and fifth ribs in the midaxillary line. Pressure on the sternum caused discomfort. Dorsiflexion of the feet caused pain, and the patient walked with a peculiar gait, throwing out the legs. No other abnormalities were found.

Extensive laboratory tests were made. The Wassermann test and the tests for blood sugar, blood urea, serum carbon dioxide content, and the serum values for chloride, potassium, sodium, cholesterol, and creatinine, all were within normal limits. The hemoglobin was 12.0 gm. per 100 ml., and the white-cell count was 5,000 cells per cubic millimeter. The total serum protein value was 6.7 gm., with albumin 2.9 gm., and globulin 3.8 gm. per 100 ml. Urinalyses were negative for the presence of sugar and albumin, and the specific gravity ranged from 1.007 to 1.020. A urinary culture was sterile; the test for Bence Jones protein was negative. Serum calcium values in two tests were respectively, 9.9 mg., and 10.0 mg. per 100 ml. (normal: 9 mg. to 11 mg. per 100 ml.). Serum phosphorus values in three tests were respectively, 2.0 mg., 1.5 mg., and 1.8 mg. per 100 ml. (normal: 2 mg. to 3.5 mg. per 100 ml.). Serum alkaline phosphatase values in two tests were respectively, 5.5, and 4.6 Bodansky units (normal: 2 to 4 Bodansky units). With the patient following the Aub controlled-calcium diet, deter-

minations of urinary calcium and phosphorus excretions were made on three 24-hour specimens. The values were:

Volume of urine in 24 hr., ml.	Excreted	Amount, mg.
1,695	Calcium	40.6
2,730	Calcium	49.1
2,032	Phosphorus	598

While the patient was following the Aub diet, reabsorption values of phosphate were respectively, 67.2 per cent and 75.57 per cent.

The results of radiographic examinations of the gallbladder, the upper gastrointestinal tract, the colon, and the genitourinary system were normal. On roentgenograms the skull appeared to be normal and the lamina dura to be intact. Radiologic examination of the skeletal system revealed pseudofractures in the right fifth, sixth, and seventh ribs, and bilaterally in the tenth and eleventh ribs, and also bilaterally at the junctions of the ischial and the pubic bodies *(Figs. 1-3)*. The diagnosis was osteomalacia secondary to renal tubular defect in reabsorption of phosphorus.

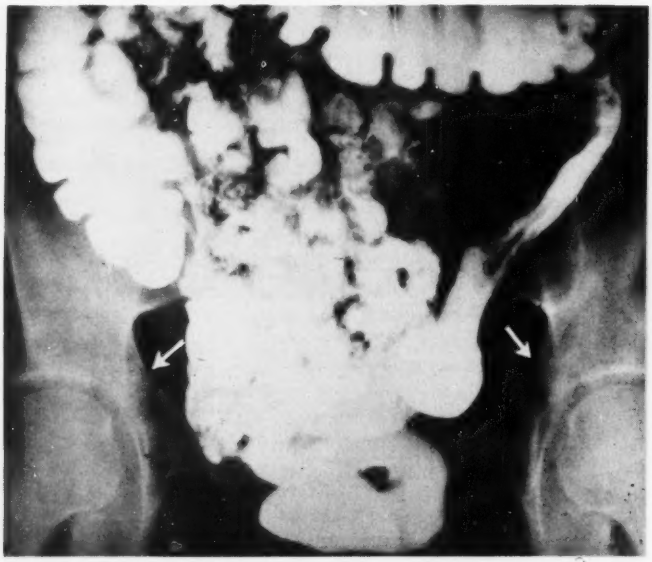

Fig. 3. Roentgenogram showing evidence of bilateral pseudofractures (arrows) at the junctions of the public and ischial bodies. The pseudofractures appear as small radiolucent notches in the cortex.

Summary

Milkman's syndrome is a form of osteomalacia. The radiolucent zones (pseudofractures) seen on roentgenograms are pathognomonic of this syndrome. The etiologic factors concerned in the development of these pseudofractures are not completely understood. A case history of Milkman's syndrome is presented.

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ERRATA

On the cover of the October, 1958, issue of this journal, the word *issue* is misspelled and the numerals for the volume and number are incorrect; they should read:

Volume 25 **Number 4**

RECENT PUBLICATIONS BY MEMBERS OF THE STAFF

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